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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,977	10/02/2003	Jack Nguyen	25840-501	9061

20985 7590 11/30/2006

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EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-16,45-48,50-54 and 56-66* is/are pending in the application.

4a) Of the above claim(s) *1-7,9,11-16,45-48,50-54 and 56-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group III, claims 63-66 and the species, granzyme B for protease and caspase for substrate in the reply filed on 9/11/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/11/2006.

Status of Claims

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66 are pending in the application.

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-63 (as it reads on the non-elected species) are withdrawn from consideration as being drawn to non-elected invention and species.

In view of the new restriction made on 4/11/2006 and applicants' election, see above, the present action supersedes the Office action mailed on 3/28/2005.

Specification

The specification is objected to because of the omission of Seq. ID. Nos. in the sequences at e.g. page 51, lines 15-20; page 22, line 15. Applicants are requested to check for other sequences in the specification since they are too numerous to mention specifically.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicants may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Written Description

The claims recite for a method of identifying a protease that cleaves a substrate sequence comprising producing a library of mutein protease sequences with each member having N mutations relative to the wild type scaffold whererin N is 1-20. To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The disclosure at the time of filing does not describe the huge scope of the claimed components of the broad claimed method steps. The claimed method steps recite only a method of producing a library of a peptide, measuring the activity of the two members of the library and identifying at least one mutein. The claims do not only cover a huge scope of the method steps but also a huge scope of the enzyme and its mutants in a library. It does not provide direction as to the kind of enzyme that can be mutagenized, the location of mutations and/or number of mutations in any of the recited enzymes. The method steps do not provide any distinguishing features of the broad claimed method steps and components employed in the method. The disclosure at page 3 recites a

diverse number of mutations made in the enzyme scaffold. It lists the different protease enzymes, pathology and target. However, a laundry list disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). The illustrative Examples, which allegedly provide a detail description of the invention, are drawn to specific method steps employing a single, defined compound species. The specification discloses that even for the specific method steps employing a specific type of protease, serine proteinases, the enzymes exhibit different substrate specificities. Some enzymes have an extended interaction site with the substrate whereas others have a specificity restricted to the P1 substrate residue. Three residues which form the catalytic triad is essential in the catalytic process i.e. His 57, Asp 102 and Ser 195. It seems likely, given the early stage of the field, that more roles exist [for caspase, a cys protease]. Caspases and caspase regulators involved in these processes may be missed in screens that focus strictly on T-5 cell death related phenotypes. Thus, molecules that possess caspase or caspase regulatory activity may not have been identified yet. For the cysteine proteases, the amino acids

selected to be modified are less well described. One therefore cannot immediately envisage from the single species the genus as claimed, as based on the disclosure above.

ENABLEMENT

Claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the mutations

that can be done to a scaffold of any protease to produce a library of muteins.

2). The specification failed to provide working examples for any of the numerous and different type of mutations in the protease or the library of muteins of such broad scope using broad method steps.

3). The breadth of the claims encompasses a large diversity of mutant enzyme, the predetermination of the sites of variations of the amino acids involve in the variation. It is well known in the art, that it is often difficult to know where insertions in the enzyme for mutations can be done without deleteriously affecting the enzyme-specificity substrate function or its global structure. The diversity of the inserts is not easily estimated for any kind of enzyme peptide.

4). The state of the prior art is such that techniques are specifically applied for a predetermined enzyme/substrate, and mutations thereof in view of the high specificity reaction of enzyme/substrate.

5). The art is inherently unpredictable because it is not possible to predict which predetermined (variations) of amino acids would result in the desired mutant with a desired pharmacologic activity. See further the discussion above. Also Harris et al (PNAS) reference e.g., at page 7754 and Legendre

(J. Mol. Biol.) at e.g., page 90, paragraph bridging col. 1 and col. 2.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous (undefined) variables of the claim would result in a mutations having a pharmacologic activity without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 63 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural

cooperative relationships of elements and essential steps, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the steps between steps (a) and (b). It is not clear as to how step (b) can occur given no step for providing a substrate or a step by which an enzyme cleaves a substrate sequence.

2. Claim 63, step © "wild-type mammalian protease scaffold" is inconsistent with the wild -type scaffold sequence of a ***human*** protease as recited in step (a). Also, it is not clear as to the difference between identifying a protease mutein having an "increased" cleavage activity from an "altered" activity, especially in the absence of positive differentiating steps between the two.

3. Claim 64 recitation of "wild-type mammalian protease scaffold" is inconsistent and at odd with the base claim 63 recitation of a "human protease scaffold". This appears to be duplicative and repetitive since the identifying step for an altered protease is not definitively recited.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koltermann et al (US 2004/0072276) in view of Waugh et al (Nature Structure Biology).

Koltermann et al discloses:

[0016] (1) a method for generating sequence-specific proteases with target substrate specificities which comprises the following steps; [0017] (a) providing a population of proteases comprised of variants of one first protease or of variants or chimeras of two or more first proteases, said first proteases having a substrate specificity for a particular amino acid sequence of a first peptide substrate; [0018] (b) contacting said population of proteases with one or more second substrates, comprising at least one specific amino acid sequence resembling the amino acid sequence of the target peptide substrate but being not present within the first peptide substrate; and [0019] (c) selecting one or more protease variants from the population of proteases provided in step (a) having specificity for said specific amino acid sequence of the second substrates provided in step (b) under conditions that allow identification of proteases that recognize and hydrolyze preferably said specific one amino acid sequence within the second substrates; [0024] The identification and selection of proteases that have evolved towards the target specificity is done by screening for catalytic activities on different peptide substrates, either by screening for increased affinity, or by using two substrates in comparison, or by using unspecific

peptides as competitors, or by using intermediate peptide substrates. The following detailed description will disclose the preferred features, advantages and the utility of the present invention.

Koltermann discloses at:

[0059] According to the invention, any protease can be used as first protease. Preferably, an endoprotease is used as first protease. It is preferred that the protease belongs to the group of proteases consisting of Serine proteases (EC 3.4.21), Cysteine proteases (EC 3.4.22), Aspartic proteases (EC 3.4.23), and Metalloproteases (EC 3.4.24). First proteases are characterized by their ability to recognize and hydrolyze peptide substrates with a certain qualitative and quantitative specificity. First proteases can have specificity in the same range as the specificity of the protease that is to be generated. Examples for proteases with relatively high specificities are TEV protease, HIV-1 protease, BAR1 protease, Factor Xa, Thrombin, tissue-type plasminogen activator, Kex2 protease, TVMV-protease, RSV protease, MuLV protease, MPMV protease, MMTV protease, BLV protease, EIAV protease, SIVmac protease. Alternatively, the first proteases have a lower specificity than the specificity of the protease that is to be generated. As an extreme example of the latter, proteases with very low sequence specificity are employed, for example proteases such as Papain, Trypsin, Chymotrypsin, Subtilisin, SET (trypsin-like serine protease from Streptomyces erythraeus), Elastase, Cathepsin G or Chymase.

See further the Examples, pages 12-14.

Koltermann does not disclose that the enzyme used in the method is granzyme B, (the elected species). However, Waugh discloses at page 762 that Granzymes are a vial component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases. Accordingly, it would have been obvious to

one having ordinary skill in the art at the time the invention was made to use granzyme as the enzyme in the method of Koltermann as taught by Waugh. One would be motivated to use granzyme for the advantage taught by Waugh above i.e., rapid cell death of a tumor.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T.D.W.

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
November 22, 2006